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10/041,977	01/09/2002	Charles A. Nicolette	GA0118USC	7476

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GENZYME CORPORATION
LEGAL DEPARTMENT
15 PLEASANT ST CONNECTOR
FRAMINGHAM, MA 01701-9322

EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
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1639	20071124

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Commissioner for Patents

The attached Examiner's Answer considers summary of the claimed subject matter, filed 8/30/2007, and merely agrees that the summary of the claimed subject matter contained in said summary is correct. No arguments, rejections, or references are added or changed.

Mark L. Shibuya, Ph.D.
Primary Examiner
Art Unit: 1639

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/041,977
Filing Date: January 09, 2002
Appellant(s): NICOLETTE, CHARLES A.

Jennifer D. Tousignant
For Appellant

EXAMINER'S ANSWER

This is in response to the summary of the claimed subject matter, filed 8/30/2007, which has been considered, and the appeal brief, filed 8/18/2006, appealing from the Office action mailed 1/21/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,510,240	LAM et al.	4-1996
5,554,724	MELIEF	9-1996

Van der Zee, R. et al. "Efficient Mapping and Characterization of a T Cell Epitope by the Simultaneous Synthesis of Multiple Peptides" Eur. J. Immunology, vol. 19, (1989), pp. 43-47.

Engelhard, V.H. "Structure of Peptides Associated with MHC Class I Molecules" Current Opinion in Immunology, vol. 6, (1994), pp. 91-95.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(a) Claims 1-2, and 4-7, 9-17, 20-23, 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Van der Zee et al.**, (European Immunology, 1989., vol. 19, pages 43-47) and **Lam et al.**, (US Patent 5,510,240).

Van der Zee et al., teach a method for efficient mapping and characterization of a T cell epitope by the simultaneous synthesis of multiple peptides. Van der Zee modifies the Pepscan method to synthesize T cell epitopes; according to the original Pepscan method small amounts of several hundreds of peptides are synthesized on activated polyethylene rods (solid supports of the instant claims) and then arrayed in a micro titer plate; after synthesis and deprotection the peptides, (referring to the library of molecules attached to solid phase supports), remain attached to the rods for subsequent analysis of their reactivity with antibodies, (i.e., B cell receptors). Van der Zee teaches that for identification and characterization of T cell epitopes, the peptides must be detached, instead, from the solid support for the screening assay. Van der Zee et al., teach that T cell clones A2b and A2c are used in T cell stimulatory activity assay.

The reference teaches that the T cell clones are incubated with the peptides which have been released from the rods, in presence of irradiated syngeneic thymocytes antigen presenting cells (APC); and the stimulatory indices are determined using the ^{3}H-thymidine incorporation. The reference also discloses that the sequence of the epitope peptides is determined; substituted peptides are prepared by single amino acid substitutions, insertions and deletions; and the analogs of the peptides are tested for activity using the same T cell clones. The reference teaches that the Pepscan method was also used to prepare a large number of epitope analogs having replacements, deletions, insertions of the residue in a nonapeptide that contain the epitope. Van der Zee et al., teach that a heptapeptide synthesized by the Pepscan method fully stimulated T cell clones. The reference compares the activity of the peptides released from the supports. The reference teaches determination of the essential residue of the epitope by synthesis of variants and determining T cell stimulation by these variants.

The claimed invention differs from the prior art teachings by using acid releasable linkers and cleaving a portion of the linker molecules such that a portion of the molecule is released. Van der Zee et al., do not teach cleaving only a portion of the linkers such that a portion of the molecule is released.

However, **Lam et al.**, teach methods of screening a peptide library. Lam et al., teach synthesis of peptides on solid phase supports using selectively cleavable linkers (referring to the releasable linkers of the instant claims) to allow sequential cleaving of the compounds from a single bead (e.g., see column 16). The reference teaches that Van der Zee et al., use aqueous formic acid (referring to acid cleaving or releasing

agent of the instant claims) as a cleaving agent in the method of characterizing of T-cell determinants. The reference teaches that the library of bio-oligomers are attached to beads with selectively cleavable linkers such that a fraction of bio-oligomers are released during each step of cleaving and that this sequential release of bio-oligomers can result from use of two different cleavable linkers or by limiting the cleavage agent or controlled irradiation (see e.g., Lam et al., at column 22). Beads from wells demonstrating biological activity are isolated and attached bio-oligomer is sequenced. Lam et al., teach that in the disclosed screening method only a small number of beads are removed during each screening step, the majority of the beads remain in the pool, and therefore the random bio-oligomer can be reused multiple times.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use selectively cleavable linkers to attach peptides to beads, as taught by Lam et al., in combination with the method of Van der Zee et al., with the expectation of identifying T cell epitopes from the library and synthesizing variants of the epitope. Because Lam et al., teach the advantages of the use of cleavable linkers, such that only a fraction of peptides are cleaved from the beads, so as to identify the T cell epitopes, as taught by Van der Zee et al.; and then still to have peptides attached to the beads, which would be useful in structure analysis methods. Van der Zee et al., teach methods of synthesis of T cell epitopes on solid phase supports and methods for identifying the T cell epitope using T cell clones and APC. Van der Zee et al., teach sequencing the positive peptides from the library and making new variant peptides using the sequence data of the positive peptides. These variants

were then tested for T cell stimulation. Thus, one skilled in the art at the time the invention was made, would have been motivated to use the methods of Lam et al., in the methods of Van der Zee with the expectation of identifying T cell epitopes and determining the structure of the epitopes and to use the information in the synthesis of T cell epitope variants which would be useful as therapeutics or in diagnosis.

(b) Claims 1-2, 4-17, 20-23, 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Van der Zee et al.**, (European Journal of Immunology, 1989, vol. 19, pages 43-47) and **Lam et al.**, (US Patent 5,510,240), as applied to claims 1-2, 4-7, 9-17, 19-28 above, and further in view of **Engelhard**, (Current Opinion in Immunology, 1994, vol. 6, pages 13-23).

Van der Zee et al., and **Lam et al.**, have been discussed supra.

The combined teachings of Van der Zee et al., and Lam et al., fail to teach the structural motif (i.e., SEQ ID NO: 1 of the instant claim 8) contained in the library of molecules.

However, **Engelhard** teaches the structure of peptides associated with MHC class I molecules. The reference teaches the recent progress in understanding the structure of major histocompatibility complex (MHC) class I molecules and the peptides to which they bind, has led to a generalized model for the peptide binding and an understanding of allele specificity. Predictions on the basis of motifs and new techniques for peptides analysis have recently resulted in the identification of several peptides that comprise peptide epitopes for antigen-specific T cells. The reference teaches that the ability of individual MHC isoforms to bind diverse arrays of peptides is based on specific interactions involving six subsites or pockets located within the deep

cleft on the top surface of the class I molecule, and the predominant length of peptides associated with most class I molecules analyzed to date is nine residues (e.g., see table 1). The reference teaches peptides which have leucine (L) and valine (V) at the terminal and six other amino acids in between (refers to instant claim 8, SEQ ID NO: 1). The reference teaches molecular cloning techniques, such as using a cDNA library, that are useful to identify epitopes recognized in databases of peptides associated with many different class I MHC molecules. The general principles that govern their binding, combined with molecular modeling would allow peptide-MHC interactions to be understood and predicted with greater certainty. The use of the existing motif information has led to the identification of several new epitopes recognized by specific cytotoxic T lymphocytes (CTLs).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the motifs disclosed by Engelhard in the methods of Van der Zee et al, and Lam et al., with the expectation of obtaining new T cell epitopes that would bind higher affinity; and using the methods of Van der Zee et al., and Lam et al., to synthesize a larger number of peptides simultaneously and screen for higher affinity T cell epitope and determining the structure of the peptide.

(c) Claims 1-2, 4-7, 9-18, 20-23, 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Van der Zee et al.**, and **Lam et al.**, (US Patent 5,510,240), as applied to claims 1-2, 4-7, 9-17, 19-28 above, and further in view of **Melief et al.**, (US Patent 5,554,724).

Van der Zee et al., and **Lam et al.**, have been discussed supra.

The combined teachings of Van der Zee et al., and Lam et al., fail to teach that the foster antigen presenting cell is from the cell line 174xCEM.T2.

However, **Melief et al.**, teach isolated tumor antigen precursor MAGE-2 derived peptides, and uses thereof. The reference teaches that these peptides bind with HLA-A2 molecule, thus presenting the complexes that provoke CTL production. The reference teaches 174xCEM.T2 line which express empty and unstable HLA-A2.1 molecules that can be stabilized when a peptide is binding to the peptide presenting grove of these molecules. The reference teaches that only a limited number of peptides bind to HLA-A2.1 with high affinity and which will be recognized by CTLs, because CTLs recognize peptides only when they are bound to HLA molecules.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use 174xCEM.T2 cell line disclosed by Melief et al., with the method of Van der Zee et al., and Lam et al., with the expectation of identifying high affinity T cell epitopes and with the expectation of using them as immunotherapeutics.

Response to Arguments From the Final Rejections, Mailed 1/21/2005

Appellant's arguments filed on 10/21/04, regarding the obviousness rejections have been fully considered but they are not persuasive.

NOTE appellant's response has addressed all the obviousness rejections together, thus the response to arguments would address the same.

Appellants argue that Van der Zee is misapplied to the presently claimed invention, and appellants traverse these rejections.

Appellants argue that Van der Zee does not teach the use of T cells, oligopeptides and antigen presenting means, each of which correspond to the same MHC haplotype restriction (see section 1 of the response).

Appellants further assert that neither Van der Zee, nor any of the cited references, teach or suggest any method to identify cytotoxic T cell epitopes wherein each of the assay components is correlated for MHC-haplotype status.

Appellant's arguments and assertions have been fully considered and are not persuasive. Appellants argue that Van der Zee does not teach the use of T cells, oligopeptides and antigen presenting means, each of which correspond to the same MHC haplotype restriction. However, the instant claims do not recite oligopeptides, and Van der Zee et al., teach that T cell stimulation usually requires processing of the protein antigen presenting cells (APC) and subsequent recognition by the T cell receptor of peptide epitopes associated with MHC present on the surface of APC. Van der Zee et al., teach the Pepscan method for synthesizing peptides (epitopes), and these peptides are cleaved from the support, since the peptides can not stimulate T cells, as T cell epitopes are only recognized in association with MHC molecules present on the APC. Thus, Van der Zee teaches that the T cells, APC and the peptides in the library share the same MHC haplotype.

Appellants further argue that 'a population of cytotoxic T cells' of the instant invention have the 'same MHC-haplotype,' only one MHC-haplotype is defined at a

time, since each MHC-haplotype is defined by a different structure, a different peptide library will be used for each agretope of the MHC-haplotype.

Appellant's arguments have been considered and are not persuasive, since the instant claims do not recite 'only one haplotype is defined at a time'; 'a different peptide library will be used for each agretope of the MHC haplotype'; and 'each released oligopeptide will correspond to the same agretope of the MHC haplotype.' In response to appellant's argument that the references fail to show certain features of appellant's invention, it is noted that the features upon which appellant relies (i.e., 'same MHC-haplotype,' only one MHC-haplotype is defined at a time, since each MHC-haplotype is defined by a different structure, a different peptide library will be used for each agretope of the MHC-haplotype) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Appellants further argue that the goal of seeking enumeration of multiple peptides capable of eliciting a cytotoxic response when complexed with a cytotoxic T cells and antigen presentation means is also not found in the prior art.

Appellant's arguments have been considered and are not persuasive, since Van der Zee et al., teach that the stimulatory activity of the T cell clones was determined by incubating the cells with various amounts of peptides in the presence of APC. Thus, peptides elicit cytotoxic response when complexed with T cells and APC.

Appellants argue that according to the teachings of Van der Zee, it would not be useful to create degenerate libraries of conserved only for MHC haplotype, because

according to Van der Zee, all native residues are seen as essential. Appellant's arguments are not persuasive for the following reasons: Van der Zee et al., teach that epitope analogues having replacements, deletions, and insertions of residues in the nonapapeptide that contains the epitope were prepared. Thus, Van der Zee teaches degenerate libraries of the conserved sequence; and the instant claims do not recite 'degenerate libraries of conserved MHC haplotype.' In response to appellant's argument that the references fail to show certain features of appellant's invention, it is noted that the features upon which appellant relies (i.e., degenerate libraries of conserved MHC haplotype) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Appellants further argue that Van der Zee created several limited libraries; all closely related to the native sequences. And further appellants discuss the invention of Van der Zee et al. Appellants argue unlike Van der Zee wherein a separate assay is conducted for each peptide species detached from individual rods which are arrayed in a microstate plate pattern by the present invention, a quantity of peptides is released from each of the solid phase supports in the library of oligopeptides.

Appellant's arguments are not persuasive, since the rejection of record is based on combined teachings of Van der Zee and Lam et al. Lam et al., teach methods of screening peptide libraries by selectively cleaving peptides from a bead.

In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellants argue that Van der Zee teaches away from the present invention (section 2 in the response).

Appellants argue that none of the Van der Zee derivatives were significantly superior to the native epitope.

Appellant's arguments that 'none of Van der Zee derivatives were significantly superior to the native epitope' are not relevant to the claimed invention.

Appellant's arguments regarding the time and energy are not persuasive, since they are not relevant to the claimed invention.

Appellant's arguments regarding the 'non-native ligands that offer improved immunological reactivity' are not persuasive, since the instant claims do not recite these limitations.

In response to appellant's argument that the references fail to show certain features of appellant's invention, it is noted that the features upon which appellant relies (i.e., non-native ligands offer improved immunological reactivity) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Appellants argue that the use of selectively cleavable linkers of Lam et al., in the method of Van der Zee et al., would neither teach nor suggest the claimed invention,

and the combination would not place the artisan in a better position than the artisan would have if employing only the method of the primary reference.

Appellant's arguments are not persuasive, since Lam et al., reference has been used to show the use of selectively cleavable linkers in the peptide library screening methods. It would have been obvious to one skilled in the art at the time the invention was made to use the selectively linkers taught by Lam et al., in the method of Van der Zee et al., with the expectation of identifying T cell epitopes and further determine the structure or sequence of the peptide epitopes. Thus, the rejections of record have been maintained.

It has been noted appellants have not addressed the rejections based on Van der Zee in view of Lam et al, Engelhard, Melief et al., of record, thus the rejections of record have been maintained.

(10) Response to Argument

Appellant appeals from the final Office action, mailed 1/21/2005, in the appeal brief, filed 8/18/2006, (hereinafter "Brief").

Appellant argues the rejections do not follow the basic tenets of obviousness analysis, which follow from Graham, and are set forth as Office policy in MPEP 2141. Appellant argues that the instant rejections under 35 U.S.C. 103(a) do not 1) consider the claimed invention as a whole; 2) the rejection rely on impermissible hindsight vision afforded by the claimed invention; and 3) the examiner has not adhered to the tenet that

the reasonable expectation of success is the standard, not "ought to be tried". Brief at pp. 6-7, bridging para, citing Graham; *Hodosh v. Block Drug Co.*, Inc., 229 USPQ 182 (Fed. Cir. 1986).

Appellant further argues the examiner has not established a prima facie case for obviousness, in accordance with Graham. The rejections fail to provide: 1) proper motivation to combine the cited references; 2) references that teach or suggest all claim limitations; and 3) reasonable expectations of success in making and using the combination of references.

a. The Office did not consider the claimed invention as a whole.

Appellant argues that the examiner impermissibly focused on a inventive concept or gist for the claimed invention, because the rejection contains "[n]o reference to a critical limitation of the instant invention, wherein each of the assay components is correlated for MHC-haplotype status and including the use of peptide libraries based upon MHC-haplotype status of the population of cytotoxic T cells to be tested", (Brief at p. 8, para 2).

Appellant's arguments filed in the Brief have been fully considered but the examiner respectfully submits that they are not persuasive.

As appellant notes, Van der Zee et al., at p. 44, col. 2, para 2, teaches the use of A2b and A2c T cell clones and syngeneic thymocytes as APC, which share the same MHC haplotype restriction. Van der Zee et al., at p. 46, Table 3, teach a library of peptides based on upon the MHC-haplotype of the cytotoxic T cells to be tested, as determined from the library of peptides of Table 2. Van der Zee et al., e.g., at p. 45, para 2, p. 47, para 2-3, Table 2, teaches peptides which comprise peptide sequences that are required for association with the MHC molecules, or with the T cell receptor or with both. Thus, the

examiner respectfully submits that Van der Zee et al., disclose and suggest methods wherein the assay components are correlated for MHC-haplotype status, including the use of peptide libraries based upon MHC-haplotype status of the population of cytotoxic T cells to be tested.

Furthermore, in response to appellant's argument that the references fail to show certain features of appellant's invention, it is noted that the features upon which appellant relies (i.e., peptides correlated for MHC-haplotype status, and peptide libraries based upon MHC-haplotype) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The examiner respectfully submits that the claims do not require that each peptide and the library be *based* upon the MHC-haplotype. Specifically, claim 1 states the limitation that the "library of molecules contains a conserved structural motif corresponding to a structural motif characteristic of peptides that associate with the MHC-haplotype to which the cytotoxic T cells are restricted", (instant claim 1, lines 9-11). Therefore, the examiner respectfully submits that the libraries, as taught by Van der Zee et al., e.g., at p. 47, para 2-3, which comprise peptides having a motif corresponding to MHC-haplotype, are libraries that contained the MHC-haplotype motif, as required by the claims.

b. The references were combined impermissibly with Hindsight

Appellant argues that improper hindsight reasoning has been employed to reject the claims. Appellant argues that the rejections do not provide detailed statements of

motivation, but rather only conclusory statements. Appellant argues that the instant rejections clearly lack a specific, motivating rationale or principle.

Appellant's arguments filed in the Brief have been fully considered but the examiner respectfully submits that they are not persuasive. In response to appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the appellant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The examiner respectfully invites the attention of the Board of Patent Appeals and Interferences to the further response set forth below.

(i) A Teaching, Motivation or Suggestion to Combine Has Not Been Identified

Appellant argues that one of ordinary skill in the art would not be motivated to combine the libraries comprising the selectively cleavable linkers of Lam et al., in the method of Van der Zee et al. First, because Van der Zee already discloses cleaving peptides from supports, appellant "wonders why an artisan would seek an alternative cleavage method where a known, successful method was provided within the reference." Second, appellant argues that the alleged "advantages" of using selectively cleavable linkers are moot, because those "alleged "advantages" are clearly taught in

the method of the Van der Zee, particularly at p. 45, col. 2, lines 6-11; at p. 47, col. 2, lines 1-4. Appellant argues that "the 'combination' would not place the artisan in a better position than the artisan would have had if employing only the method of the primary reference", (Brief at p. 10). Appellant argues that because of this "clear failure of Van der Zee", it unmistakably follows that there is no motivation to combine Van der Zee et al., with the references of Engelhard or with Melief et al.

Appellant's arguments filed in the Brief have been fully considered but the examiner respectfully submits that they are not persuasive. The examiner respectfully submits that Van der Zee et al., provides motivation that is specific for combining particular species of linkers (i.e., linkers comprising aspartic acid-proline bonds) within the genus of linkers, as taught by Lam et al., (col. 16, col. 22, lines 32-59, and as in instant claim 1. *Compare*, Lam et al., at col. 16, especially line 40; Van der Zee et al., at p. 44, para 4; instant Specification at p. 27, para [077]; disclosing acid cleaving of aspartic acid-proline bonds in linkers linking peptides with solid supports).

Lam et al., at col. 16, lines 14-28, disclose using various linkers and modifications thereof, "to meet specific requirements for the particular purpose of bioassay or detection." Lam et al., at col. 22, line 36-41, teaching the use of two different cleavable linkers to release only a portion of bio-oligomer. The examiner respectfully submits that one of ordinary skill in the art would have been motivated to combine the teaching of the cited references, because Lam et al., teach the desirability

of using various linkers, including selectively cleavable linkers, beyond those taught by Van der Zee.

(ii) The Primary Reference Teaches Away from the Suggested Combinations

First, appellant argues that none of Van der Zee's "derivatives" were significantly superior to the native epitope, so that one of ordinary skill in the art would not be motivated to prepare or analyze derivative epitopes.

Second, appellant argues that there is no reason to expend significant time and energy to create libraries of peptides sharing the same MHC-haplotype in a broad search for non-native epitopes, because the reference of Van der Zee et al., teaches variations upon the native epitope, (Brief at p. 11). Appellant states:

> Notwithstanding the efforts to date to identify T cell epitopes, the inventor has recognized a clear need in the art for a rapid method to identify cytotoxic T cell epitopes. In several cases, derivatized natural epitopes are more effective than the natural epitope itself, accordingly, there is a need to identify such derivatized natural epitopes.

Brief at p. 11, para 5.

Appellant's arguments filed in the Brief have been fully considered but the examiner respectfully submits that they are not persuasive.

Firstly, appellant argues limitations, (i.e., derivative epitopes that are superior to the native epitope and derivatized natural epitopes), which are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification,

limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Secondly, Van der Zee et al., teach synthetic nonapeptides linked to polyacrylic polymer rods, and thereby teach non-native epitope production. Van der Zee teaches 28 peptides (see e.g., p. 45, Table 2) and contemplate automizable procedures, such as the Pepscan method, that can test several hundreds of synthetic peptides (Van der Zee at p. 43, para 2), in order to establish the identity of epitopes, thereby teaching derivatized epitopes. Van der Zee, at p. 43, para 3, teaches and suggests modification of the Pepscan method to identify and characterize T cell epitopes in proteins with known sequences.

Furthermore, Van der Zee considers the impact that contaminating peptides introduced during solid phase synthesis would have on identifying T cell epitopes, and finds that "generally these contaminants are not likely to interfere during epitope scanning of a protein sequence by this methods", (Van der Zee at p. 46, para 6), thus suggesting further studies. Van der Zee et al., at p. 47, para 4, state that "[t]he rapidly acquired qualitative T cell response to peptides prepared by this method may enhance the progress of T cell epitope determination studies, and we expect that this method is equally well suited for the identification of T cell epitopes using polyclonal T cells." Therefore, the examiner respectfully submits that Van der Zee e al., suggests creating libraries of peptides sharing the same MHC-haplotype in a broad search for T cell epitopes.

c. The References Do Not Teach All Elements of the Claimed Invention

i) Van der Zee Does Not Teach T Cells, Oligopeptides and Antigen Presenting Means, Each of Which Correspond to the Same MHC-Haplotype Restriction

Appellant argues that the references teach or suggest any method to identify cytotoxic T cell epitopes wherein each of the assay components is correlated for MHC-haplotype status. Appellant argues that "[t]he correlated cytotoxic T cells, library of molecules and antigen presentation means permits complete testing of a less complex library with the goal of finding a range of active molecules, including but not limited to the native sequence." Brief at p. 12, para 2.

Appellant states:

> Moreover, since Van der Zee's assay relies upon syngeneic thymocytes as antigen presentation means (see, Van der Zee at Section 2.2), it would not be necessary for Van der Zee to correlate the MHC status of the cytotoxic T cells, the oligopeptides and the antigen presentation means. By definition, a syngeneic system is from the same organism. Thus, syngeneic thymocytes have a repertoire of all the necessary antigen presentation means for each T cell tested, and therefore, need not be matched for MHC-haplotype.

Brief at p. 13, para 2.

Appellant argues that the concept of using peptide libraries based upon MHC-haplotype status of the population of cytotoxic T cells to be tested is not found in the reference of Van der Zee et al. See, Brief at p. 12, para 4.

Appellant argues that "the goal of seeking enumeration of multiple peptides capable of eliciting a cytotoxic response when complexed with a cytotoxic T cell and antigen presentation means is not found in the prior art", (Brief at p. 12, para 5). Appellant argues "if one were to make libraries based upon the teachings of Van der

Zee, they would contain only one difference per peptide as compared with the native antigen. Van der Zee uses degenerately designed sequences to sequentially study the contribution of each native residue", (Brief at p. 13, para 3).

Appellant argues that the "instant inventor determined that it would be possible to detect activity elicited from individual species even in a pooled fraction of peptides", (Brief at p. 14, para 1), unlike the teaching of Van der Zee et al., wherein a separate assay is conducted for each peptide species detached from individual rods which are arrayed in a microtiter plate pattern. See Brief at p. 14, para 1.

Appellant's arguments filed in the Brief have been fully considered but the examiner respectfully submits that they are not persuasive.

Van der Zee et al., necessarily disclose the use of cytotoxic T cells, library of molecules and antigen presentation means, otherwise Van der Zee would not have been able to effect activation of MHC-restricted T cell clones (see, e.g., Van der Zee at p. 45, Table 1). Van der Zee explicitly contemplates such restriction (see, e.g., Van der Zee at p. 43, para 1 and p. 47, para 1-3).

Furthermore, the reference of Engelhard, at e.g., p. 13, para 1, teaches the generation of MHC-associated peptides from the newly synthesized proteins of cells that have been infected by intracellular parasites or that have undergone transformation, to allow recognition and cellular destruction by T lymphocytes.

Appellant argues limitations, i.e., enumeration of multiple peptides capable of eliciting a cytotoxic response that is not recited in the rejected claims. The claims

require the activation of cytotoxic T cells, but do not require assaying the *cytotoxicity* of the activated T cells. Furthermore, Van der Zee, e.g., at Tables 2 and 3, teaches an enumeration of multiple peptides in epitope libraries.

Appellant argues limitations, i.e., detection activity elicited from individual species even in a pooled fraction of peptides, which is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

ii) Van der Zee Does Not Teach Cytotoxic T Cell Activation

Appellant argues that the claimed method requires cytolytic activity of T cells. Appellant notes that the teachings of Van der Zee do not teach or suggest cytolytic T cell activity or lysis of antigen presentation means, but rely upon a T cell stimulatory assay.

Appellant's arguments filed in the Brief have been fully considered but the examiner respectfully submits that they are not persuasive.

Appellant argues limitations not found in the claims. The claims do not require a cytolytic assay, but only the detection activation of cytolytic T cells. Although the claims are interpreted in light of the specification, limitations from the specification are not read

into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, the cited reference of Melief et al., at Example 3, col. 8, line 45-col. 10, line 34, and Fig. 2, teach cytotoxic T cell assays involving peptides derived from tumor cells that bind to HLA-A2 MHC molecules, with antigen presenting cells, to provoke cytolytic T cell cytolysis. Melief et al., at col. 11, line 7-col. 12, line 17, suggests that the polypeptide so identified may be used for prophylaxis, diagnosis and treatment of cancer cells.

Also, Van der Zee, at p. 44, para 5, teaches activation of T cell clones A2b and A2c. The A2b cells and A2c cells are cytotoxic T lymphocytes, as evidenced by the instant Specification, which teaches the cloned CTL line of Van der Zee to be a cloned CTL line that is used in a CTL stimulation assay. The instant Specification states:

> [0017] **Van der Zee (1989, Eur. J. Immunol., 19:43-47)** and coworkers have developed a powerful but limited strategy for identifying T-cell epitopes. Briefly, utilizing the "pepscan" technique, they were able to simultaneously synthesize several dozens of peptides on polyethylene rods arrayed in a 96-well microtiter plate pattern. This is similar to an indexed library in that the position of each pin defines the synthesis history on it. Peptides were then chemically cleaved from the solid support and supplied to irradiated syngeneic thymocytes for antigen presentation. **The cloned CTL line was then tested for reactivity** in a proliferation assay monitored by ^{3}H-thymidine incorporation. This type of analysis particularly suits a CTL stimulation assay since it can be automated using a microtiter plate reader and employs relatively low levels of radiation. The procedure successfully identified a reactive epitope in a defined region of a 65 kDa mycobacterial heat shock protein with essentially no background. A second screen where the synthesized peptides had one alanine insertion per peptide at each position of the naturally occurring epitope identified an additional seven peptides with diminished yet detectable reactivity, underscoring the tolerances to substitutions in this assay. Additionally, screening peptides having a single deletion per peptide (derived from the

> natural epitope) yielded no reactive peptides, underscoring the specificity endowed by the presence of the nine residues in the naturally occurring epitope.

Specification at para [0017], (emphasis added).

d. There Was No Reasonable Expectation of Success in Combining the References

Appellant argues that no reasonable expectation of success can exist because the cited references fail to provide all of the elements of the claimed invention.

> Appellant's arguments filed in the Brief have been fully considered but the examiner respectfully submits that they are not persuasive. The examiner respectfully submits that cited references, taken as whole, teach and suggest the elements of the claimed invention, as discussed above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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